bonded via a bridging member,

-Met-Ile-Glu-Gly-Arg-,

to a peptide which stabilizes the fusion protein;

(b) liberating a mini-proinsulin compound from said fusion protein by cleaving the expressed fusion resulting from step (a) with cyanogen bromide to produce mini-proinsulin;

(c) incubating the product formed in step (b) with sodium tetrathionate to form hexa-5-sulfonate;

(d) simultaneously incubating the S-sulfonate mini-proinsulin formed in step (c) with trypsin and carboxypeptidase at a pH of about 6.8 under conditions where no crystals are formed; and

(e) precipitating the insulin.--

REMARKS

Claims 21-23 and 25-27 are pending in this application. New claim 31 is presented herein. This claim clarifies that the claimed process for producing insulin does not yield undesirable byproducts such as DES-B30 which is a common byproduct of the prior art processes.

Applicants note that the objection to the specification and rejection of claims 21-23 and 25-27 under 35 U.S.C. § 112, first paragraph, has been withdrawn. In an Amendment filed August 2, 1996, claims 21, 22, 25 and 26 were amended to incorporate the phrase "under conditions where no crystals are formed." In Paper No. 35, the Examiner rejected this

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amendment as being "new matter." This rejection is respectfully traversed and the amendment is resubmitted herein.

It is a well established tenet of Patent Law that the specification need not describe the claimed invention using the identical words found in the claims in order to satisfy the requirements of 35 U.S.C. § 112. Martin v. Johnson, 172 U.S.P.Q. 391, 395 (C.C.P.A. 1972). Furthermore, in Tektronix, Inc. v. United States, 165 U.S.P.Q. 392, 394 (Court of Claims 1970), the court ruled that it is not new matter to amend the specification and drawings to make explicit a disclosure which was implicit in the application as filed. It is respectfully submitted that it would be readily apparent from the specification to one of ordinary skill in the art that no crystals are formed under the described experimental conditions. For example, pages 15-16 disclose that trypsin digestion which converts mini-proinsulin to mono-Arg-insulin, takes place in an aqueous buffer which does not contain phenol or other aromatics. This reaction mixture is precipitated using $ZnCl_2$, and the mono-Arg-insulin precipitate is purified by crystallization using a buffer containing phenol. Therefore, the reaction product is obtained as a precipitate and not in the form of crystals as evidenced by the disclosed crystallization step. Thus, the amended claims do not incorporate new matter; rather, the claim language merely makes explicit that which is implicitly disclosed in the specification.

Rejection Under 35 U.S.C. § 103

Claims 21-23 and 25-27 are rejected as allegedly unpatentable over Markussen *et al.* (U.S. Patent No. 4,916,212 and EP 0153,529) (hereinafter "Markussen references") in view of Goeddel *et al.*, Mai *et al.*, and Grau (U.S. Patent Nos. 4,801,684 and 4,639,332).

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The Examiner alleges that the claimed invention is obvious because Markussen *et al.* ('212):

> [D]iscloses and claims insulin precursors of the form B(1-29)-X_n-Y-A(1-21). "X" is a peptide chain with n amino acids, "n" is an integer from 0 to 33, and "Y" is Lys or Arg. X is preferably selected from the group consisting of Ala, Ser, and Thr. A preferred embodiment is B(1-29)-Ser-Lys-A(1-21). This precursor protein is a single peptide chain. This precursor is converted to human insulin by derivatization and treatment with trypsin. . . . Fusion proteins and their cleavage from the precursor are disclosed. . . . DNA sequences encoding the insulin precursor, expression vectors, transformed yeast cells, and recombinant methods of production in yeast (as well as E. coli holding plasmids encoding the desired insulin precursors) are also disclosed and claimed.

See Office Action page 3, lines 4-15 (citations omitted).

The Examiner further contends that one of ordinary skill in the art would be motivated to practice the claimed invention because Grau discloses the exceptional stability of the mono-Arg-insulin. See Office Action page 3, line 18 through page 4, line 3.

Applicants respectfully disagree. The pending claims are drawn to a process for preparing mono-Arg-insulin and human insulin. As discussed above, the reaction conditions are such that the process takes place in an aqueous buffer wherein crystals of the intermediary products are not obtained. Further, the claimed process permits simultaneous addition of trypsin and carboxypeptidase to the reaction mixture.

The Markussen references do not disclose the claimed reaction process. As stated in previous responses, the human insulin precursor, or the starting material, disclosed by the Markussen references can be represented by a generic formula encompassing a very large number of species. There is no teaching in the art that could motivate the skilled artisan to select the mini-proinsulin of formula I as the starting material to produce insulin. In addition, the

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Markussen references do not disclose or suggest the reaction steps of the claimed process. Nor do they disclose formation of the mono-Arg-insulin as an intermediary product.

Furthermore, the process disclosed by the Markussen references requires transpeptidation of the precursor with L-threonine esters in the presence of trypsin or trypsin derivatives. The insulin esters so obtained have to be hydrolyzed to obtain mature insulin. These additional steps further complicate the prior art reaction process. In stark contrast, the claimed invention represents a simple process which does not require the transpeptidation and hydrolyzation steps of Markussen.

The Examiner has argued that the skilled artisan would be motivated to practice the claimed invention because Grau is asserted to show the stability of the mono-Arg-insulin. However, the process disclosed by Markussen does not teach the formation of mono-Arg-insulin, or its subsequent conversion to insulin. Thus, contrary to the Examiner's assertion, there is no reason why the skilled artisan would be motivated to use the process disclosed by Markussen to produce insulin via production of mono-Arg-insulin as an intermediate. Mere knowledge of the existence of mono-Arg-insulin does not provide the requisite motivation to modify the process disclosed by Markussen. It is well known in the art that there are numerous methods of synthesizing insulin, each method in turn results in the production of various intermediate products, some of which may be exceptionally stable like the mono-Arg-insulin produced herein. However, mere knowledge of such intermediate products would not provide the skilled artisan the motivation or the know-how to modify their reactions procedures to obtain mono-Arg-insulin.

To summarize, the Markussen references fail to

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(a) teach or suggest the starting material used in the claimed process;

(b) teach or suggest the formation of mono-Arg-insulin as an intermediate; and

(c) fail to teach or suggest the simultaneous addition of trypsin and carboxypeptidase.

The Examiner asserts that one of ordinary skill in the art would have been motivated to use the precursor of insulin with the formula of Markussen *et al.* wherein X is Thr, n is 1, Y is Arg, and m is 1, in order to obtain mono-Arg-insulin of Grau. The Examiner further contends that "Grau provides motivation to obtain mono-Arg-insulin because of its stability, thereby making obvious the species of X = Thr, n=1, Y=Arg, and m=1 in Markussens' generic formula." Office Action page 5, lines 2-7.

It is respectfully submitted that the Examiner is using improper hindsight in making this rejection. The Federal Circuit has cautioned against such non-obviousness rejections and ruled that:

> It is error to reconstruct the patentee's claimed invention from the prior art by using the patentee's claim as a "blueprint." When prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight obtained from the invention itself.

Interconnect Planning Corp. v. Feil, 227 U.S.P.Q. 543 (Fed. Cir. 1985). In this case, the Examiner selects Grau because the reference discloses mono-Arg-insulin and concludes that the skilled artisan would use the starting material and process disclosed by Markussen to obtain the mono-Arg-insulin disclosed by Grau, although there is no teaching or suggestion which would enable the skilled artisan to modify the process disclosed by Markussen in order to obtain the mono-Arg-insulin. The main objective of Markussen was to obtain human insulin and not

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precursors to human insulin. Thus, there is no reason why one would modify the Markussen process to yield mono-Arg-insulin.

Additionally, the Examiner states that the starting material used by Markussen would be obvious in light of the intermediate disclosed by Grau. Clearly, this is an improper effort at reconstructing the claimed invention by piecing together the references of record. The Federal Circuit has expressly held, that "there must be some logical reason apparent from positive, concrete evidence of record which justifies a combination of primary and secondary references" (emphasis added). In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989). In the instant case, there is no logical reason which justifies the combination of the references.

The Examiner further asserts that it would have been obvious to use both trypsin and carboxypeptidase B to convert the mini-proinsulin of Markussen first to mono-Arg-insulin and then to insulin. Office Action page 6, lines 10-12.

Once again, there is no teaching or suggestion in the prior art which would lead to the simultaneous use of these enzymes. The prior art of record does not suggest a process wherein mono-Arg-insulin may be converted to insulin by simultaneous action of these enzymes. Grau ('684) discloses a process for obtaining insulin precursors from reaction mixtures resulting from the folding of insulin precursors from their corresponding sulfonates. See column 5, lines 30-65. The claimed process step is neither taught, disclosed, or suggested by the prior art.

Finally, in Paper No. 29, it was argued that "[t]he limitation of conditions where no crystals are formed would be met as the prior art does not absolutely require crystallization and furthermore, the methods do not preclude additional steps where crystallization occurs." This contention is untenable.

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It is respectfully submitted that the cited art fails to support the above contention. The reaction conditions disclosed by Grau ('684) necessarily result in the formation of crystals of mono-Arg-insulin. Grau states that "[t]he desired product precipitates out of the reaction solution in sharp-edged prisms about 5-20μm in size". See column 4, lines 40-42. The enzymatic cleavage step disclosed by Grau occurs close to the isoelectric point of insulin in the presence of aromatics. As a result there is a direct precipitation of the cleavage product into crystalline form. In other words, the process described in the cited art will always result in a crystalline product. This feature is an important benefit of the disclosed process because it leads to a product which is resistant to further digestion. Therefore, Grau teaches away from the claimed process and fails to render the claims obvious.

Furthermore, the deficiencies of Markussen and Grau are not remedied by Goeddel or Mai. These references do not teach or suggest the claimed process for obtaining mono-Arg-insulin and insulin. Thus, it is respectfully submitted that the Office has failed to present a *prima facie* case of obviousness.

CONCLUSION

Reconsideration and withdrawal of this rejection is respectfully requested.

If there are any fees required in connection with the filing of this Response the Commissioner is hereby authorized to charge any additional fees (or credit any overpayment)

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associated with this response to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such extension is requested and should also be charged to our Deposit Account.

Respectfully submitted,

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